We recently attended a Key Opinion Leader event focused on the treatment of interstitial lung disease (ILD). The event featured a presentation from Dr. Steven Nathan, who is the Director of the Advanced Lung Disease Program and Lung Transplant Program at Inova Fairfax Hospital, and a Professor of Medicine at the Virginia Commonwealth University Inova Campus. In addition, event sponsor Bellerophon Therapeutics (NasdaqGM: BLPH) provided an update on its ILD program using pulsed inhaled nitric oxide (iNO). A replay of the event is available here. Bellerophon recently reported data from a Phase IIa study using its INOpulse drug device in pulmonary hypertension associated idiopathic pulmonary fibrosis (PH-IPF). An IND for pulmonary fibrosis (PF) was recently accepted by the FDA, and the Company plans to initiate a Phase IIb study in ILD early next year, with topline data coming in 2018.

- **IPF is Often Confused with ILD.** Interstitial lung diseases (ILDs) are a broad class of acute and chronic lower respiratory tract disorders. Patients with ILD commonly present with stereotypical clinical and physiological features including shortness of breath, decreased lung function, and decreased oxygen flow to the lungs at times of rest and exertion, resulting in hypoxemia. ILD is thought to arise from an unknown tissue injury that results in aberrant lung tissue repair in people that are predisposed to the disease. A hallmark of the disease is honeycombing at the base of lungs viewed via a high-resolution chest CT, which according to Dr. Nathan, can be enough to make a diagnosis.

  Idiopathic pulmonary fibrosis (IPF) is a type of ILD that falls under idiopathic interstitial pneumonias (IIP). Work done by Dr. Nathan's group and others suggests that IPF makes up about a third of all cases of ILD. IPF is often accompanied by complications due to the development of pulmonary hypertension (PH), a chronic condition characterized by high blood pressure in the lungs that can lead to right heart failure. PH is divided into 5 distinct groups according to the World Health Organization (WHO). ILDs fall into group 3, which includes lung-related diseases such as IPF. Although there are two therapies approved to treat the fibrosis associated with IPF, there are no approved therapies for PH associated with group 3 ILDs.

- **High Clinical Unmet Need for Patients with IPF.** Prior to the approval of anti-fibrotic therapies, pirfenidone and nintedanib, the median survival for patients with IPF was approximately 46 months. Anti-fibrotic agents slow the progression of the disease but are not curative. This is important since IPF and other ILDs can at some point become complicated by the development of PH. In fact, Dr. Nathan pointed out that 38% of IPF patients have PH at baseline. As patients progress toward needing lung transplantation, the proportion of IPF patients with PH increases, reaching roughly 90%. Although systemic vasodilators have been approved for the treatment of some PH associated diseases, such as pulmonary arterial hypertension (PAH), there are no approved therapies for lung-related disorders classified under the group 3 criteria. This represents a high unmet clinical need that could potentially be addressed by therapies targeting the PH component of the disease.

- **IPF Poses a High Economic Burden on the Healthcare System.** ILD is a disease primarily affecting the elderly, and its prevalence is steadily increasing in the US. According to Dr. Nathan, the increase in prevalence could be linked to incidental discovery due to the expanded use of CT scans. Although the exact prevalence of ILD is hard to estimate, Dr. Nathan believes the population could be as much as 400,000. Studies done by Dr. Nathan's group and others suggest that IPF represents roughly 30% of ILDs. The annual incidence of IPF in the US Medicare population is estimated to be 94 per 100,000 and constitutes a significant economic burden on the healthcare system. In fact, a study performed in the US showed that the average direct cost for patients with IPF was two times that of matched healthy individuals. Based on the prevalence of the disease, this amounts to more than $1 billion in healthcare spending annually.

- **Evidence for Inhaled NO as a Treatment Option for ILD.** Pulmonary arterial pressure (PAP) is a key prognostic factor in patients with IPF. For example, the median overall survival in patients with mean PAP (mPAP) ≥25 mmHg is about 2 years compared to roughly 6.5 years in patients a mPAP of ≤ 25 mmHg. However, multiple studies with therapeutic agents that reduce PAP have shown minimal to no clinical benefit in PH-IPF. This was mainly due to an increase in ventilation perfusion mismatch. Matching ventilation and vessel perfusion is required to achieve proper arterial oxygenation. Dr. Nathan highlighted two key features of Bellerophon's inhaled NO...
(iNO) that could be beneficial for the treatment of PH-ILD. First, the inhaled therapy acts locally, avoiding systemic effects of other vasodilators. Second, iNO reduces pulmonary pressure while improving arterial oxygenation in the lung.

- **Pulsed iNO as a Complementary Therapy to Approved Anti-Fibrotic Treatments.** PH associated IPF is thought to stem from the dysregulation of multiple pathways. While other drugs in this therapeutic space target the fibrosis aspect of the disease, Dr. Nathan emphasized the possibility of using multimodal and combination therapies in the future as a way to address the complexity of the disease. For example, patients with PH-IPF could conceivably be placed on an anti-fibrotic agent, for treatment of fibrosis. iNO could then be used either before or after the development of PH to mitigate the disease. Of note, iNO therapy could potentially be used to treat other ILDs, such as non-specified interstitial pneumonia.

- **Efficacy of Bellerophon’s INOpulse in a Phase IIa Trial of PH-IPF.** Bellerophon conducted a proof of concept Phase IIa study that evaluated pulsed iNO in patients with PH-IPF. A total of four patients were enrolled to receive pulsed iNO using the Bellerophon’s INOpulse delivery system, along with oxygen therapy. This was a two-part study that included a dose titration portion and a chronic treatment portion. Patients in the dose titration portion of the trial received either 75 µg/kg ideal body weight (IBW)/hr (iNO 75) or 30 µg/kg IBW/hr (iNO 30) of iNO for 20 minutes and subsequently underwent a high resolution CT scan. Two of the four patients entered the chronic treatment portion of the study, and continued on iNO therapy plus long-term oxygen therapy (LTOT) for four weeks. The primary endpoint for the study was a change in airflow distribution and hemodynamics, and the secondary endpoint was six-minute walk distance (6MWD). The Company also measured distance saturation product (DSP), a composite measure that takes into account oxygen saturation and distance during 6MWD. DSP has been shown to be a better predictor of mortality in IPF compared to either oxygen saturation or spirometry.

Pulsed iNO was well tolerated at iNO 30 and resulted in select vasodilation of blood vessels in well-ventilated areas. The study met its endpoint, demonstrating an average 15% increase in blood vessel volume from baseline (p<0.001) in all four patients treated with pulsed iNO, and patients also experienced an average 14% reduction in systolic pulmonary arterial pressure (sPAP). The Company reported a 50 meter improvement in 6MWD as well as a 75% improvement in DSP in patients treated with iNO 30 for four weeks, providing preliminary evidence that pulsed iNO therapy can benefit patients with PH-IPF and perhaps patients with other ILDs.

- **Planned iNO-PF Phase IIb in ILD.** This double-blinded randomized study is expected to enroll approximately 40 patients with ILDs including IPF, non-IPF IIP, and patients with either occupational/environmental lung disease or chronic hypersensitivity pneumonitis. The trial will evaluate pulsed iNO 30 µg/kg IBW/hr (iNO 30) + LTOT compared to placebo in patients with ILD. As shown in Figure 1, patients will undergo a 1-week run-in period with the drug device to ensure treatment compliance, and will then be randomized to receive either iNO 30 or placebo for 8 weeks total. 6MWD will be measured at baseline, at week 4, and then again at week 8. After 8 weeks of treatment, patients are allowed to continue on open-label iNO treatment with periodic assessments every 4 months. Patient selection and grouping will be performed using echocardiography, which will allow the Company to categorize patients into those with either high or low probability of developing PH. This is important since it expands the population included in the study relative to the Phase IIa study.
The primary endpoint of the trial will be the change in 6MWD and the secondary endpoint will be the change in right ventricular function assessed by echocardiography. These endpoints were confirmed by the FDA in June and the Company’s IND for treatment of pulmonary fibrosis with iNO was recently accepted. Bellerophon will also explore other endpoints including distance saturation product (DSP), dyspnea, and shortness of breath. Dr. Nathan was optimistic about the likelihood of success for this trial, since pulsed iNO was efficacious in treating PH-IPF during the Phase IIa study, is well tolerated, and can be evaluated in a short time period. The data from this study will be important for the potential of pulsed iNO therapy in ILDs.

**Risk to Investment**

We consider an investment in Bellerophon to be a high-risk investment. Bellerophon is a development stage company with no history of taking a treatment to market and currently has no FDA approved drugs in its portfolio. The Company’s clinical programs have not yet completed Phase III trials. Furthermore, early indications of efficacy do not necessarily translate into positive late-stage results. Ongoing clinical trials will result in significant additional expenses to the Company and may require additional rounds of dilutive financing. As with any company, Bellerophon may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any drug and Bellerophon may not receive FDA approval for its candidate despite significant time and financial investments. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations.
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